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What is the Prognostic Value of Myocardial Perfusion Imaging Using Rubidium-82 Positron Emission Tomography?

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OBJECTIVES The objective was to determine the prognostic value of rubidium-82 (^{82}Rb) positron emission tomography (PET) myocardial perfusion imaging (MPI).

BACKGROUND ^{82}Rb PET MPI accurately diagnoses coronary artery disease (CAD). However, there are limited data evaluating its prognostic value.

METHODS Follow-up (3.1 ± 0.9 years) was obtained in 367 patients who underwent dipyridamole ^{82}Rb PET MPI. Patients were divided into groups based on their summed stress score (SSS): group I, normal (<4); group II, mild (4 to 7); and group III, moderate (8 to 11) to severe (≥12).

RESULTS There were significant differences among patients in the 3 SSS groups for hard events (cardiac death and myocardial infarction [MI]) ($p < 0.001$) and total cardiac events (hard events, revascularization and hospitalization) ($p < 0.001$). The annual hard events rates were 0.4%, 2.3%, and 7.0% in the normal, mild, and moderate-severe groups, respectively. In adjusted survival models, ^{82}Rb PET SSS was the strongest predictor of total cardiac events and a significant predictor of hard events. Among patients referred for PET after ^{99m}Tc single-photon emission computed tomography, the annual total event rate was higher with abnormal versus normal SSS on PET (15.2% vs. 1.3%, $p < 0.001$). In patients with obesity, the annual total event rate was 11.1% with an abnormal scan and 1.5% with a normal scan ($p < 0.001$).

CONCLUSIONS This study shows that ^{82}Rb PET MPI has significant prognostic value for predicting cardiac events, including death and MI. It also seems to have prognostic value in patients whose diagnosis remains uncertain after single-photon emission computed tomography MPI and in obese patients. The prognostic value of PET MPI may improve the management of cardiac patients. (J Am Coll Cardiol 2006;48:1029–39) © 2006 by the American College of Cardiology Foundation

Risk stratification of patients with suspected or documented coronary artery disease (CAD) identifies patients at risk for future cardiac events. Myocardial perfusion imaging (MPI) using single-photon emission tomography (SPECT) has shown good prognostic value (1–4), and patients with a normal SPECT MPI have a low hard cardiac events rate (<1%/year) (5–7).

Positron emission tomography (PET) MPI has been widely used as an accurate means to diagnose CAD (8–14). Rubidium-82 (^{82}Rb) is a PET perfusion tracer produced from a strontium-82 (^{82}Sr)/^{82}Rb generator and is widely used in centers without immediate access to a cyclotron (9,11,13–16). Rubidium-82 PET MPI is highly specific and sensitive for the diagnosis of CAD (11,13,14,17–19). However, data supporting the prognostic value of ^{82}Rb PET MPI are limited (20). The primary goal of the current study was to evaluate the prognostic value of ^{82}Rb PET imaging for the prediction of cardiac events.

Although SPECT MPI is a highly useful noninvasive diagnostic modality for the detection of CAD, clinicians are sometimes faced with equivocal or nondiagnostic results. Patients with equivocal scans have increased risk compared with a normal population (21). Further risk stratification of these patients is often required. Rubidium-82 PET MPI may be clinically useful for this indication (22). However, data to support this approach are in fact quite limited, and no studies have evaluated the prognostic value of PET MPI in such patients. A secondary objective of this study was to evaluate the prognostic value of ^{82}Rb PET MPI among a subset of patients referred for ^{82}Rb PET imaging after SPECT perfusion imaging.

The prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) has dramatically increased since 1990 with >20% of the U.S. adult population being reported as obese (23,24). Obesity has a significant adverse impact on cardiovascular morbidity (25,26). Obese patients require accurate diagnostic tools for the evaluation of their cardiac risk. Current

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Abbreviations and Acronyms

BMI = body mass index
CABG = coronary artery bypass grafting
CAD = coronary artery disease
MI = myocardial infarction
MPI = myocardial perfusion imaging
PCI = percutaneous coronary intervention
PET = positron emission tomography
^{82}Rb = rubidium-82
SDS = summed difference score
SPECT = single-photon emission computed tomography
SRS = summed rest score
SSS = summed stress score

modalities often have diagnostic difficulties in the obese population (27–30). Although PET MPI is often applied in patients with obesity, its prognostic value in this population has not been well studied. An additional secondary objective of the current study was to evaluate the prognostic value of ^{82}Rb PET MPI in a subset of patients with obesity.

METHODS

Study population. The study population was composed of 448 consecutive adult patients (age >18 years old) who underwent dipyridamole stress ^{82}Rb PET MPI between January 1, 2000, and October 31, 2000, at the University of Ottawa Heart Institute. Patients with known nonischemic cardiomyopathy or significant valvular heart disease were excluded. Of the 448 patients, 37 (8.3%) patients were lost to follow-up and 33 (7.4%) patients, although contacted, declined to participate in the follow-up study. The remaining 378 patients were enrolled in the study.

Because abnormal scans can result in early revascularization and potentially alter outcome, 11 (2.9%) patients with early revascularization (in the first 3 months after ^{82}Rb PET MPI) were excluded from the prognostic portion of the analysis. Similar approaches have been applied in previous studies (2,3,31,32). Thus, the prognostic data presented in the current study are based on a population of 367 patients.

The study was approved by the University of Ottawa Heart Institute Human Research Ethics Board. Informed consent was obtained from all subjects. In cases in which patients died before follow-up, consent was obtained from the next of kin.

PET acquisition protocol. Patients were positioned in a whole-body PET scanner (ECAT ART, Siemens/CTI Knoxville, Tennessee), a 4-min transmission scan was performed for attenuation correction (33). Immediately after the transmission scan, 400 to 2000 MBq (8 MBq/kg) of ^{82}Rb was administered intravenously over 1 min. A 7.5-min acquisition was initiated 2.5 min after tracer administration (14,33–36).

Dipyridamole myocardial perfusion ^{82}Rb PET imaging. Patients were instructed to fast for ≥6 h and to abstain from caffeine-containing products for >12 h before pharmacological stress. After the rest ^{82}Rb PET imaging, a pharmacological stress test was performed with the infusion of dipyridamole (0.14 mg/kg/min over 5 min). Stress imaging was acquired using the identical protocol as the rest imaging. The ^{82}Rb (400 to 2,000 MBq [8 MBq/kg]) was infused 3 min after completion of the dipyridamole infusion (33,35,36). During dipyridamole stress, symptoms, heart rate, blood pressure, and the electrocardiogram were monitored continuously.

PET image interpretation. Regional myocardial perfusion was assessed using the 17-segment model recommended by the Cardiac Imaging Committee of the American Heart Association and the American Society of Nuclear Cardiology (36,37). Each segment was scored by two expert observers blinded to clinical data using a five-point scoring system (0 = normal, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced, 4 = absent uptake) (36,38,39). Differences between observers were settled by a third observer. The sum of segment scores at stress (summed stress score [SSS]), scores at rest (summed rest score [SRS]), and differences between stress and rest score (summed difference score [SDS]) were calculated (4). Patients were divided into groups based on their SSS (3,4,14,21). Because we used a 17-segment model according to American Society of Nuclear Cardiology recommendation (36), we adjusted the validated SPECT 20-segment model scoring to be equivalent percentages of the total possible score in the myocardium. Thus, a scan was considered normal if the SSS was <4, mildly abnormal if SSS was between 4 and 7, moderately abnormal if SSS was between 8 and 11, and severely abnormal if SSS was ≥12. This normal/abnormal cutoff represents a similar percentage of the myocardium used as a cutoff score in previous PET studies (14). The moderately abnormal and severely abnormal groups were combined because of the small number of patients in the moderately abnormal group. The SSS was the primary focus of our analysis.

Patients were also divided into groups based on their SDS combined with their SSS: patients with a SDS ≥2 were considered to have myocardial ischemia; patients with an SDS <2 with normal SSS were considered normal; patients with SDS <2 but abnormal SSS were considered to have scar without ischemia.

Image quality was evaluated by two experts blinded to clinical or other imaging data and scored on a three-point scale: suboptimal = 0 (artifact such that a definitive conclusion could not be made), fair = 1 (an artifact but interpretation was made), good = 2 (conclusive interpretation).

Patient follow-up. Patient follow-up was performed using a scripted telephone interview by health care professionals blinded to the patient's MPI data. The mean follow-up period was 3.1 ± 0.9 years. Cardiac events were confirmed using the best information that was available. Hard cardiac events were defined as either cardiac death (confirmed by review of death certificate, hospital chart, or physician's records) or nonfatal MI (considering the appropriate combination of elevated cardiac enzymes, electrocardiogram

changes, and ischemic symptoms, from hospital chart or physician's records). Late (>3 months) revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]) or the need for other hospitalization for cardiac causes (e.g., unstable angina, chest pain, heart failure) other than MI were defined as other cardiac events. Hence total cardiac events were a composite of cardiac death, nonfatal MI, late revascularization, and cardiac hospitalization.

If the patients had hard cardiac events, patients in the study only had one hard cardiac event, death or nonfatal MI. For total cardiac events, some patients had two or more events (e.g., nonfatal MI and revascularization). In such patients, the first event date was considered for the survival analysis.

Subgroup populations—patients referred for PET after SPECT MPI. To further evaluate the prognostic value of ^{82}Rb PET MPI, we assessed the subgroup of patients with recent ^{99m}Tc SPECT MPI. The goal of this ancillary subgroup analysis was to evaluate the prognostic value of ^{82}Rb PET MPI in cases of patients referred after SPECT, in which uncertainty about the diagnosis remained either based on the SPECT report or in which SPECT findings did not support the clinical impression. Clinical SPECT MPI reports were reviewed by two observers blinded to ^{82}Rb PET imaging data to categorize SPECT image findings and image quality.

A subgroup of 102 patients was identified who had had SPECT MPI within 6 months before ^{82}Rb PET MPI studies. Among these, one patient who had unstable angina between SPECT and ^{82}Rb PET MPI was excluded. Two patients had early revascularization. These two patients were included in image quality analysis but excluded from the secondary outcome analysis. Five patients with thallium-201 (^{201}Tl) SPECT MPI were also excluded. In addition, four patients had clear-cut moderate-severe abnormalities on SPECT that had similar location, extent, and severity of defect as their ^{82}Rb PET MPI studies. These patients were included in the ^{99m}Tc SPECT versus ^{82}Rb PET image quality analysis but excluded from the secondary outcome analysis, so as not to bias the prognostic value data in favor of PET. Therefore, the subgroup was composed of 96 patients for image quality and 90 patients for secondary outcome analysis, who were referred for PET after ^{99m}Tc SPECT MPI.

Among these 96 patients, 50 patients had exercise; 45 had dipyridamole stress ^{99m}Tc SPECT MPI, and 1 had rest SPECT imaging but did not get dipyridamole because of very poor image quality at rest, rendering the images equivocal.

^{99m}Tc SPECT imaging. The SPECT MPI was performed at either the University of Ottawa Heart Institute (n = 92) or other referring institutions (n = 10). For ^{99m}Tc SPECT MPI studies, a same-day, rest-stress ^{99m}Tc tetrofosmin or ^{99m}Tc sestamibi injection protocol was used. For the rest studies, tomographic imaging was initiated 30 to 45 min after 296 to 370 MBq of ^{99m}Tc tetrofosmin or ^{99m}Tc sestamibi tracer injection. The ^{99m}Tc tomographic images were obtained using a standard 30-min 180° SPECT acquisition protocol (40).

The stress study was performed approximately 120 min after the rest imaging. For patients who underwent symptom-limited treadmill exercise using the Bruce protocol, a dose of 925 to 1,110 MBq of ^{99m}Tc tetrofosmin or ^{99m}Tc sestamibi was injected at peak exercise and the patients continued exercise for an additional 1 to 2 min. For those who underwent dipyridamole stress testing, 3 min after the completion of dipyridamole (0.14 mg/kg/min over 5 min), tracer was injected intravenously. Tomographic imaging was initiated 30 to 45 min after the tracer injection. The same acquisition protocol for rest was used for stress (40). Based on clinical reports, a similar protocol was followed for the patients referred from other institutes.

Image quality and diagnostic certainty with ^{99m}Tc SPECT and ^{82}Rb PET MPI. All clinical SPECT reports were reviewed. Image quality was classified as described for ^{82}Rb PET MPI; suboptimal = 0, fair = 1, good = 2.

Regarding diagnostic certainty of the images, reports that were definitively indicated as normal or abnormal were considered conclusive, whereas diagnostic uncertainty was defined as studies in which reports were not conclusive and were considered to be probably normal, equivocal, or probably abnormal (41). Diagnostic certainty was scored as conclusive = 1 or uncertainty = 0. A total of 96 patients were evaluated for image quality and diagnostic certainty analysis.

PET MPI in patients with obesity. There are limited data on the value of MPI in patients with obesity (defined as BMI ≥30 kg/m^2) (42); thus, we further evaluated the prognostic value of PET MPI in this subgroup.

The mean BMI of our study population was 30.0 ± 14.3 kg/m^2. There were 134 (36.5%) patients with BMI ≥30 kg/m^2 (obese), 136 (37.1%) patients with BMI 25 to 29.9 kg/m^2 (overweight), and 97 (26.4%) patients with a BMI <25 kg/m^2 (normal). The subgroup population for this ancillary analysis was the obese population (n = 134).

Statistical analysis. Continuous measures are presented as means ± SD. For the univariable analysis of differences, Wilcoxon rank sum tests were used for continuous measures. Categorical measures are presented as frequencies with percentages. Frequencies were compared using Fisher exact tests for the univariable analysis.

The prognostic value of SSS for unadjusted as well as adjusted hard (cardiac death and MI) and total cardiac event rates were assessed for the full population. All unadjusted comparisons of event rates were based on survival analysis log-rank tests. Annual event rates were calculated by dividing the 3-year Kaplan-Meier event rates by 3.

For the risk-adjusted analysis, multivariable Cox proportional hazard models were used to assess the independent prognostic value of the SSS controlling for baseline patient characteristics and creating adjusted survival curves. To

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prevent overfitting of the model, the number of variables considered for modeling were reduced by combining the coronary risk factors (hyperlipidemia, hypertension, diabetes, smoking, family history of CAD) into one variable (>2 coronary risk factors). Also to limit the number of variables, the baseline variables that showed significance in the univariable analysis were considered individually with SSS in the model. From this testing, for the hard cardiac events, age >65 years, history of MI, and known CAD met the threshold for entry of $p < 0.05$. These variables were considered together in the stepwise selection of the final multivariable model for hard cardiac events (cardiac death and MI), which included only three covariates (SSS, age >65 years, and history of MI). For total cardiac events, men, history of MI and CABG, known CAD, angina symptoms, and patients with two or more coronary risk factors met the threshold for entry of $p < 0.05$. These variables were considered together in the stepwise selection of the final multivariable model for total cardiac events, which included four covariates (SSS, gender [male], history of MI, and two or more coronary risk factors).

The multivariable models with and without SSS were produced to determine the incremental value of SSS. A statistically significant increase in the global chi-square value of the models with SSS defined an incremental prognostic value of SSS. The percent of contribution of each covariate to the global chi-square value was also reported to show the relative importance of the variables in the hard (cardiac death and MI) and total cardiac events models.

For the secondary analyses of the subgroups populations, the small number of events combined with the small sample size in the subgroups limited the ability to perform the multivariable analysis. Thus, only unadjusted survival analysis was performed for these subpopulations.

The concordance between ^{82}Rb PET and ^{99m}Tc SPECT MPI for classifying the image quality and diagnostic certainty was determined using kappa statistics. The mean image quality score was compared using the Wilcoxon signed rank test. The comparison of diagnostic certainty of the images (conclusive = 1, uncertainty = 0) was performed using the McNemar test.

A p value < 0.05 was considered statistically significant. Statistical calculations were carried out using SAS software (version 9.1.2, SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient characteristics. The baseline characteristics of the 367 patients who comprised the study population are shown in Table 1. The characteristics of the patients who were lost to follow-up were all similar to the study population (p = NS), including mean age (57.6 ± 14.2 years), gender (40.5% male), and SSS distribution (normal, 26 [70.3%]; mild, 4 [10.8%]; moderate to severe, 7 [18.9%]).

Outcome events. Among the 367 patients in this study, there were 11 (3.0%) cardiac deaths and 6 (1.6%) nonfatal MIs. A total of 29 (7.9%) patients underwent late revascularization (PCI alone [n = 19], CABG alone [n = 8], or both PCI and CABG [n = 2]). A total of 16 (4.4%) patients were hospitalized for cardiac causes (other than revascularization or MI). Fifty-nine patients (16.1%) suffered a total of 62 cardiac events (2 patients had nonfatal MI and late revascularization and 1 patient had late revascularization and cardiac death on greatly separated dates).

Table 1. Baseline Patient Characteristics

	Patients With Follow-Up (n = 367)
Age (yrs)	59.4 ± 10.9
Gender (male)	168 (45.8%)
Height (m)	1.7 ± 0.1
Weight (kg)	83.5 ± 47.2
BMI (kg/m^2)	30.0 ± 14.3
Obese	134 (36.5%)
Patient follow-up time (yrs)	3.1 ± 0.9
History of MI	113 (30.9%)
History of CABG	45 (12.3%)
History of PCI	74 (20.2%)
Known CAD	148 (40.3%)
Angina symptoms (CCS class ≥2)	184 (54.3%)
CHF (NYHA functional class ≥II)	20 (5.7%)
Coronary risk factors	
Hyperlipidemia	211 (58.0%)
Hypertension	187 (51.2%)
Diabetes mellitus	60 (16.4%)
Smoking	224 (63.5%)
Family history of CAD	164 (44.8%)
Summed stress score	
Normal	259 (70.6%)
Mild	44 (12.0%)
Moderate	13 (3.5%)
Severe	51 (13.9%)

Obese was defined as BMI ≥30 (kg/m^2) (42). Data are presented as mean ± SD or number (%) of patients.

BMI = body mass index; CABG = coronary bypass grafting; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

Univariable analysis of baseline demographics for cardiac events. The results of univariable analysis of baseline demographics (not including PET parameters) are summarized in Table 2. Patients with hard cardiac events (cardiac death and nonfatal MI) were older, were more often male, and had a greater history of MI or CABG, known CAD, angina symptoms, and diabetes mellitus. Patients with any cardiac event were older, were more often male, and had a greater history of MI, CABG, PCI, known CAD, angina symptoms, coronary risk factors (2 or more), diabetes mellitus, and smoking.

Stress perfusion ^{82}Rb PET abnormalities and outcomes. Cardiac events during follow-up as a function of the SSS severity are shown in Table 3. The rates of both hard (cardiac death and nonfatal MI) and total cardiac events increased with increasing severity of SSS. The respective annual hard cardiac event rates were 0.4%, 2.3%, and 7.0% in patients with: 1) normal, 2) mildly, and 3) moderate to severely abnormal SSS on ^{82}Rb PET MPI. The annual total

Table 2. Baseline Patient Characteristics by Cardiac Death/Nonfatal MI and Total Cardiac Events

	Death/Nonfatal MI			Total Events		
	Patients With Event (n = 17)	Patients With No Event (n = 350)	p Value*	Patients With Event (n = 59)	Patients With No Event (n = 308)	p Value*
Age >65 yrs	12 (70.6%)	99 (28.3%)	<0.001	26 (44.1%)	85 (27.6%)	0.014
Gender (male)	13 (76.5%)	155 (44.3%)	0.012	47 (79.7%)	121 (39.3%)	<0.001
History of MI	15 (88.2%)	98 (28.1%)	<0.001	41 (69.5%)	72 (23.5%)	<0.001
History of CABG	7 (41.2%)	38 (10.9%)	0.002	19 (32.2%)	26 (8.4%)	<0.001
History of PCI	5 (29.4%)	69 (19.8%)	0.354	21 (36.2%)	53 (17.2%)	0.002
Known CAD	16 (94.1%)	132 (37.7%)	<0.001	46 (78.0%)	102 (33.1%)	<0.001
Angina symptoms	13 (81.3%)	171 (52.9%)	0.037	45 (79.0%)	139 (49.3%)	<0.001
CHF	2 (13.3%)	18 (5.3%)	0.205	4 (7.1%)	16 (5.4%)	0.536
Patients with >2 coronary risk factors	10 (58.8%)	149 (42.6%)	0.215	38 (64.4%)	121 (39.3%)	<0.001
Hyperlipidemia	6 (37.5%)	205 (58.9%)	0.120	38 (65.5%)	173 (56.5%)	0.246
Hypertension	11 (64.7%)	176 (50.6%)	0.323	36 (61.0%)	151 (49.4%)	0.118
Diabetes mellitus	8 (47.1%)	52 (14.9%)	0.003	16 (27.1%)	44 (14.4%)	0.021
Smoking	14 (87.5%)	210 (62.3%)	0.060	47 (83.9%)	177 (59.6%)	<0.001
Family history of CAD	6 (35.3%)	158 (45.3%)	0.465	26 (44.1%)	138 (45.0%)	1.000
Obese	7 (41.2%)	127 (36.3%)	0.797	20 (33.9%)	114 (37.0%)	0.768

*Fisher exact test.
Abbreviations as in Table 1.

cardiac event rates were 1.7%, 12.9%, and 13.2%, respectively. Unadjusted survival free of hard cardiac events including cardiac death and nonfatal MI were significantly different among the SSS groups (cardiac death, $p < 0.001$; MI, $p = 0.002$; hard cardiac events, $p < 0.001$) (Table 3). Unadjusted survival free of any cardiac events was also significantly different among the SSS groups ($p < 0.001$) (Table 3).

Multivariable Cox models of risk-adjusted outcomes. The results of multivariable analysis for cardiac events to assess the independent prognostic value of the SSS score controlling for baseline patient characteristics are summarized in Table 4. The model including ^{82}Rb PET SSS showed its independent prognostic value for the hard cardiac events ($p = 0.016$) after controlling for the significant covariates age >65 years and history of MI. Of these variables, the strongest predictors (based on contribution to the hard cardiac event model) were age >65 years and ^{82}Rb PET SSS. Considering the models with and without SSS, the significant increase in global chi-square for the SSS model showed the incremental prognostic value of the ^{82}Rb PET SSS.

The model including ^{82}Rb PET SSS showed its independent prognostic value for the total cardiac events ($p < 0.001$) after controlling for the significant covariates men, history of MI, and two or more coronary risk factors. Of these variables, the strongest predictor (based on contribution to the total cardiac event model) was ^{82}Rb PET SSS. The incremental prognostic value of ^{82}Rb PET SSS was also shown by the total cardiac events models with and without SSS.

Adjusted survival curves illustrate that SSS groups were significantly different for hard cardiac events (cardiac death and nonfatal MI) (Fig. 1A) and total cardiac events (Fig. 1B).

Ancillary and subgroup analysis—myocardial ischemia and outcomes. The prognostic value of SDS at follow-up is shown in Table 5. Patients were divided into three groups: group I, normal (normal SDS and SSS); group II, ischemia (SDS ≥2); group III, scar without ischemia (SDS <2; abnormal SSS). The unadjusted survival free of hard cardiac events (cardiac death and nonfatal MI) was significantly different among patients with scar without ischemia (group III), those with ischemia (group II), and those with normal SSS and no ischemia (group I) ($p < 0.001$ for hard cardiac events, $p < 0.001$ for cardiac death). Ischemia-related events (nonfatal MI and late revascularization) were significantly different among pa-

Table 3. Cardiac Events Over the Follow-Up Period for Different Summed Stress Scores

	n	Death	NFMI	Revasc (Late)	Hosp	Death or NFMI	Death or NFMI AER	Total Events	Total Events AER
Normal	259	1 (0.4%)	2 (0.8%)	7 (2.7%)	5 (1.9%)	3 (1.2%)	0.4%	15 events in 14 patients (5.4%)*	1.7%
Mild	44	2 (4.6%)	0 (0.0%)	12 (27.3%)	4 (9.1%)	2 (4.6%)	2.3%	18 (40.9%)	12.9%
Moderate and severe	64	8 (12.5%)	4 (6.3%)	10 (15.6%)	7 (10.9%)	12 (18.8%)	7.0%	29 events in 27 patients (42.2%)†	13.2%
Log-rank test p value		<0.001	0.002	<0.001	<0.001	<0.001		<0.001	

*One patient had nonfatal myocardial infarction and late revascularization. †One patient had late revascularization and cardiac death. One patient had nonfatal myocardial infarction and late revascularization.
AER = annual event rate; Hosp = hospitalization; NFMI = nonfatal myocardial infarction; Revasc = revascularization.

Table 4. Multivariable Cox Proportional Hazard Models for Cardiac Death/Nonfatal MI and Total Cardiac Events Showing the Incremental Prognostic Value of Summed Stress Score

Model	Variable	p Value	Percent of Global Chi-Square Value	Global Chi-Square Value
Cardiac death/nonfatal MI				
Baseline	Age >65 yrs	0.006	32.8	23.06
	History of MI	<0.001	59.8	
Baseline + SSS	Age >65 yrs	0.011	22.5	28.73*
	History of MI	0.036	15.3	
	Summed stress score	0.016	20.4	
Total cardiac events				
Baseline	Gender (male)	<0.001	27.1	58.63
	History of MI	<0.001	37.2	
	Patients with >2 coronary risk factors	0.005	13.7	
Baseline + SSS	Gender (male)	0.001	15.0	72.13†
	History of MI	0.027	6.8	
	Patients with >2 coronary risk factors	0.006	10.3	
	Summed stress score	<0.001	16.2	

*Significant increase in global chi-square ($p < 0.05$). †Significant increase in global chi-square value ($p < 0.001$).
SSS = summed stress score; other abbreviations as in Table 1.

tients with ischemia (group II), those with scar without ischemia (group III), and those with normal SSS and no ischemia (group I) ($p = 0.034$ for MI, $p < 0.001$ for late revascularization).

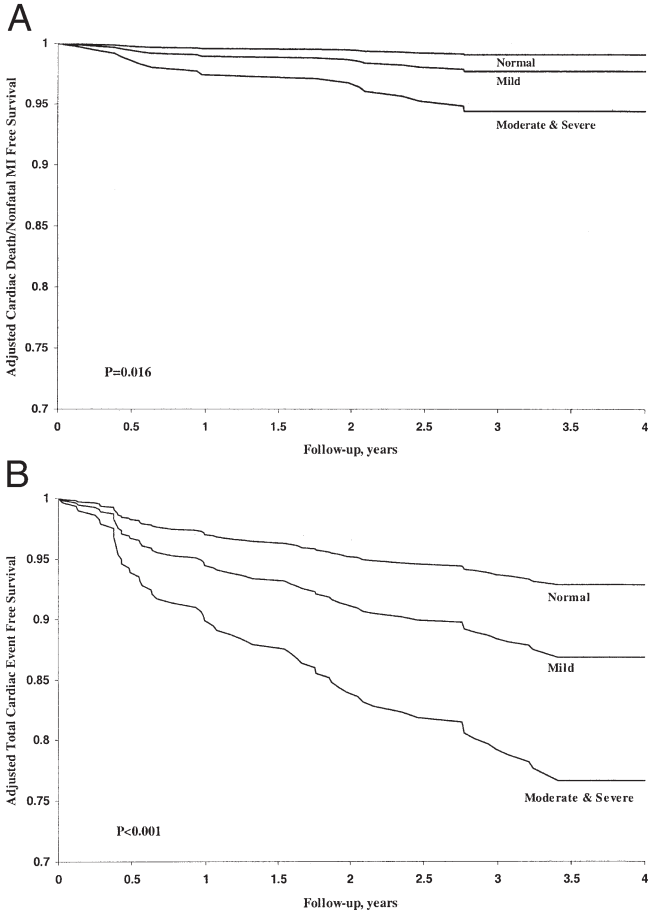

Figure 1. (A) Risk-adjusted survival, free from hard cardiac events (cardiac death and nonfatal myocardial infarction), as a function of summed stress score (SSS). **(B)** Risk-adjusted survival, free from any (total) cardiac events, as a function of SSS.

Ancillary and subgroup analysis—patients referred for PET after SPECT MPI. PATIENT CHARACTERISTICS. We assessed the subgroup of patients with recent ^{99m}Tc SPECT MPI to determine the image quality and diagnostic certainty ($n = 96$) and the prognostic value of ^{82}Rb PET MPI ($n = 90$) in patients referred after SPECT in whom uncertainty about the diagnosis remained.

Compared with the main study cohort, the patients who were referred for PET after ^{99m}Tc SPECT were younger, had less history of revascularization, had less known CAD, and had less severe SSS compared with the total cohort (total cohorts vs. SPECT patients: age, 59.4 ± 10.9 vs. 56.6 ± 9.8 years [$p = 0.023$]; history of CABG, 12.3% vs. 3.3% [$p = 0.012$]; history of PCI, 20.2% vs. 5.6% [$p < 0.001$]; known CAD, 40.3% vs. 23.3% [$p = 0.003$]; SSS distribution [$p = 0.002$], respectively). There was a trend for less history of MI ($p = 0.051$).

These patients had high BMI similar to the total cohort. There was no significant difference in gender between the two cohorts (gender [male], 45.8% vs. 48.8%, $p = 0.638$). There was also no significant difference in other parameters, including follow-up time, angina symptoms, chronic heart failure class, and coronary risk factors (p = NS).

IMAGE QUALITY COMPARISON BETWEEN ^{99m}Tc SPECT AND ^{82}Rb PET MPI. In this specific study population, the overall concordance of image quality between ^{99m}Tc SPECT and ^{82}Rb PET MPI was 22% (21 of 96, kappa = 0.02) (Table 6). The image quality was superior in PET compared with SPECT. The mean quality score of PET was 1.94 ± 0.24, and that of SPECT was 0.71 ± 0.78 ($p < 0.001$).

DIAGNOSTIC CERTAINTY OF IMAGING COMPARISON. In this specific study population, the overall concordance for the diagnostic certainty of the images between ^{99m}Tc SPECT and ^{82}Rb PET MPI was 22% (21 of 96, kappa = 0.01) (Table 6). The diagnostic certainty of the image

Table 5. Cardiac Events Over the Follow-Up Period for Ischemia and Summed Stress Score

	n	Death	NFMI	Revasc (Late)	Hosp	Death or NFMI	Death or NFMI AER	Total Events	Total Events AER
Group I No ischemia Normal SSS	254	1 (0.4%)	2 (0.8%)	7 (2.8%)	5 (2.0%)	3 (1.2%)	0.4%	15 events in 14 patients (5.5%)*	1.7%
Group II Ischemia	94	6 (6.4%)	4 (4.3%)	21 (22.3%)	8 (8.5%)	10 (10.6%)	4.2%	39 events in 37 patients (39.4%)†	12.2%
Group III No ischemia Abnormal SSS	19	4 (21.1%)	0 (0.0%)	1 (5.3%)	3 (15.8%)	4 (21.1%)	8.7%	8 (42.1%)	14.0%
Log-rank test p value		<0.001	0.034	<0.001	<0.001	<0.001		<0.001	

*One patient had nonfatal myocardial infarction and late revascularization. †One patient had late revascularization and cardiac death. One patient had nonfatal myocardial infarction and late revascularization.
Abbreviations as in Tables 3 and 4.

(conclusive versus uncertainty) was superior using PET compared with SPECT ($p < 0.001$).

CARDIAC EVENTS IN PATIENTS REFERRED FOR PET AFTER SPECT MPI. Among the 90 patients included in the outcome analysis, 11 (12.2%) patients had an abnormal ^{82}Rb PET SSS (8 mildly abnormal and 3 severely abnormal) and 79 patients had a normal SSS.

During follow-up, there were a total of 11 cardiac events: 1 nonfatal MI, 7 late revascularizations, and 3 cardiac hospitalizations. One patient had both a nonfatal MI and late revascularization. Thus, 10 patients (11.1%) suffered at least one cardiac event.

Among 11 patients with an abnormal ^{82}Rb PET SSS, 7 patients had a cardiac event with a high annual total cardiac event rate (15.2%), compared with 3 patients suffering a cardiac event in those with normal ^{82}Rb PET MPI, for an annual total cardiac event rate of 1.3%. Unadjusted survival free of any (total) cardiac events was significantly different between normal and abnormal SSS groups ($p < 0.001$) (Fig. 2).

Table 6. Image Quality Comparison and Diagnostic Certainty of Image Comparison Between ^{99m}Tc SPECT and ^{82}Rb PET MPI

	SPECT		
PET	Suboptimal	Fair	Good
Image quality comparison			
Suboptimal	—	—	—
Fair	4	2	0
Good	43	28	19

	SPECT		
PET	Diagnostic Uncertainty	Normal	Abnormal
Diagnostic certainty of image comparison			
Diagnostic uncertainty	—	—	—
Normal*	40	15	25
Abnormal	7	3	6

Image quality agreement: 21/96 (22%), kappa = 0.02. Diagnostic certainty of image agreement: 21/96 (22%), kappa = 0.01. *No significant defect (i.e., summed stress score <4).
MPI = myocardial perfusion imaging; PET = positron emission tomography; SPECT = single photon emission tomography.

PROGNOSTIC VALUE OF PET MPI IN PATIENTS WITH OBESITY. Among the 134 patients with obesity, 45 (33.6%) had an abnormal ^{82}Rb SSS (15 mildly abnormal, 8 moderately abnormal, and 22 severely abnormal) and 89 patients had a normal SSS.

During follow-up, there were a total of 22 cardiac events: 5 cardiac deaths, 2 nonfatal MIs, 8 late revascularizations, and 7 cardiac hospitalizations occurred in 20 patients. In the subgroup of 134 obese patients, 45 patients with an abnormal SSS had 7 hard cardiac events, with a high annual hard cardiac event rate (6.0%) compared with 0% in those with normal ^{82}Rb PET MPI (Table 7). Unadjusted survival free from hard cardiac events was significantly different between normal and abnormal SSS groups ($p < 0.001$).

Similarly, among 45 patients with an abnormal SSS, 18 total cardiac events occurred in 16 patients, with a high annual total cardiac event rate (11.1%) compared with 4 total cardiac events in those with normal ^{82}Rb PET MPI, for an annual total cardiac event rate of 1.5% (Table 7). Unadjusted survival free of any (total) cardiac events was

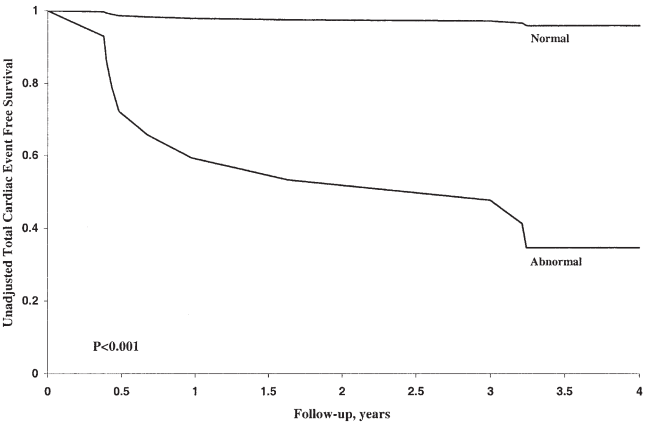

Figure 2. Unadjusted survival, free from any (total) cardiac events, as a function of normal and abnormal summed stress score on positron emission tomography (PET) myocardial perfusion imaging (MPI) in patients referred for PET after recent single-photon emission computed tomography MPI.

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Table 7. Cardiac Events in Obese Patients

	n	Death	NFMI	Revasc (Late)	Hosp	Death or NFMI	Death or NFMI AER	Total Events	Total Events AER
Normal	89	0 (0.0%)	0 (0.0%)	1 (1.1%)	3 (3.4%)	0 (0.0%)	0	4 (4.5%)	1.5%
Abnormal	45	5 (11.1%)	2 (4.4%)	7 (15.6%)	4 (8.9%)	7 (15.6%)	6.0%	18 events in 16 patients (35.6%)*	11.1%
Log-rank test p value		<0.001	0.025	<0.001	0.135	<0.001		<0.001	

*One patient had late revascularization and cardiac death. One patient had nonfatal myocardial infarction and late revascularization.
Abbreviations as in Table 3.

significantly different between normal and abnormal SSS groups ($p < 0.001$) (Fig. 3).

DISCUSSION

These results show that in this population, the rates of both hard cardiac events (death and nonfatal MI) and other cardiac events increase with severity of ^{82}Rb PET stress MPI results. Normal ^{82}Rb PET MPI indicates an excellent prognosis with an annual hard cardiac event rate of 0.4%. Multivariable analysis indicates an independent prognostic value of the ^{82}Rb PET SSS.

In subgroup analyses the data suggests that in patients with recent SPECT MPI and in those with obesity, ^{82}Rb PET MPI has prognostic value and is able to identify higher-risk patients.

Prognostic value of PET MPI. The PET MPI has high spatial and temporal resolution compared with other nuclear imaging techniques (11,16). It yields high sensitivity and specificity for the detection of CAD (11,18,19,43). However, data supporting the prognostic value of PET MPI are limited.

One previous study by Marwick et al. (20) evaluated the prognostic value of ^{82}Rb PET MPI in a population composed mostly of patients with known CAD (70%). They showed that ^{82}Rb PET defect severity was associated with cardiac death and total events rates. Mortality rates for normal and abnormal defects were 0.9% per year and 4.3% per year. Our current study supports the notion that cardiac events increase with the severity of ^{82}Rb PET MPI SSS. However, the two studies differ in patient population and event rates. In the study by Marwick et al. (20), most of the patients (70%) had CAD, a large number (22%) of patients had early revascularization, and normal perfusion on PET MPI was present in only 24%. In contrast, the current study, 71% of patients had normal stress perfusion and 2.9% patients had early revascularization. Thus, Marwick et al. (20) studied a higher-risk population than did our current study. This higher-risk population may not reflect the patients for whom PET has been suggested to be most useful and cost-effective, namely those with a low and intermediate pretest likelihood of CAD (44).

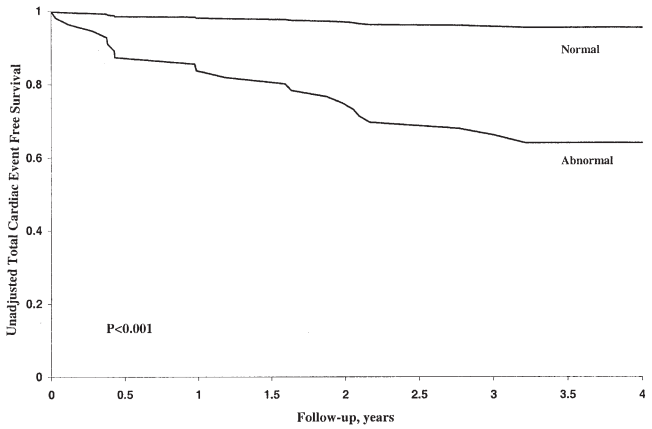

Figure 3. Unadjusted survival free from any (total) cardiac events as a function of normal and abnormal summed stress score on PET MPI in patients with obesity (body mass index ≥30 kg/m^2). Abbreviations as in Figure 2.

Our patient population more closely resembles recent SPECT study populations in which 20% to 50% of patients had known CAD (3,6,21,32,45,46) and early revascularization rates of <7% (3). In the current study, 40% of patients were known to have CAD, which may explain the lower event rates and lower early revascularization rate compared with the study by Marwick et al. (20). Our data indicate that the extent of ^{82}Rb PET MPI SSS has prognostic value and applicability in a lower-risk patient population. Also of note, the current study showed that in the adjusted survival models, ^{82}Rb PET MPI SSS was the strongest predictor of total cardiac events and was also a significant predictor of hard cardiac events.

Marwick et al. (20) reported that ischemia was not related to cardiac death and total cardiac events, which they attributed to their high early revascularization rate (22%) among patients with ischemia. This high revascularization rate made it more difficult to evaluate the prognostic value of ischemia on ^{82}Rb PET MPI. In the present study, the cardiac death rate was significantly higher in patients with fixed defects (scar) compared with patients with ischemia or normal scans. However, ischemic events (nonfatal MI and late revascularization) were greater among the ischemic group. The current data suggest that the extent of ischemia as identified by ^{82}Rb PET MPI may also provide useful prognostic information.

We have recently reported a very low hard cardiac event rate (0.2% over 27 months of follow-up; 0.09% per year) in a group of patients with ^{82}Rb PET MPI clinically reported as normal (47). This very low event rate differs from the current study and is attributed to: 1) a more strict definition

of normal (based on clinical reports); 2) shorter follow-up; and 3) exclusion of patients with left bundle branch block or ventricular pacing, in the previous study. In addition to the longer follow-up, broader inclusion criteria, and use of SSS, the current study also evaluated the prognostic value of abnormal SSS on PET MPI.

The current study also differs from previous work and is unique because it evaluates the prognostic value in important subgroups in which PET may have additional value, namely in patients whose diagnosis remains uncertain after SPECT MPI and in patients with obesity.

Prognostic value of SPECT MPI. The prognostic value of exercise and pharmacological SPECT MPI has been well established (5–7). Previous SPECT studies showed annual hard event rates of 0.2% to 0.8% for a normal SPECT MPI study (2,3,21). The demographics and SSS in the current study are similar to those of previous SPECT studies (2,3,21). Also, the increasing event rate with worsening defect size along with the excellent event free survival in patients with normal PET MPI are consistent with those of previous SPECT studies (2–4,21,45).

Previous SPECT MPI studies showed that cardiac death is better predicted by extent of myocardial scar, whereas myocardial ischemia seems to predict ischemic events (6,32,48). Similar findings were observed in the current study for PET MPI.

Prognostic value of PET in patients referred after SPECT MPI. An equivocal SPECT MPI study is an American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology guidelines Class 1 indication for the use of PET MPI (22). This recommendation was based on consensus given the advantages of PET imaging. However, studies evaluating this approach have been limited. MacIntyre et al. (49) reported that patients who had false-negative ^{201}Tl SPECT but true positive ^{82}Rb PET had a significant change in their treatment strategies. However, to our knowledge, there has been no previous study evaluating the prognostic value of PET in the clinical setting when the diagnosis remains uncertain after SPECT MPI. The importance of this group of patients has been evaluated by Berman et al. (21), who reported that an equivocal SPECT study was associated with increased cardiac events and thus these patients may require additional risk stratification. In the current study, a subgroup of 90 patients whose diagnosis remained uncertain after ^{99m}Tc SPECT MPI was evaluated and had been referred for ^{82}Rb PET MPI. In this subgroup, the annual total cardiac event rate was higher in patients with abnormal ^{82}Rb PET MPI SSS than in those with normal PET MPI (15.2% vs. 1.3%). Unadjusted survival from total cardiac events was significantly different between normal and abnormal PET MPI SSS groups ($p < 0.001$). This study provides data to support the consensus opinion in the American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology guidelines for PET MPI. Further outcome studies in this population are required.

In this specific subpopulation of the current study, the image quality concordance between ^{82}Rb PET MPI and ^{99m}Tc SPECT MPI was poor. Image quality was superior with ^{82}Rb PET compared with ^{99m}Tc SPECT MPI. In these selected patients, the added value of PET likely reflects its accuracy and its ability to correct for attenuation. Attenuation-corrected SPECT MPI is currently applied in limited centers (50). New methods of attenuation correction are being developed for both SPECT and PET. These may further improve diagnostic accuracy and prognostic value for both modalities. Further studies are needed to evaluate these evolving approaches.

Prognostic value of PET in obesity. Accurate diagnostic tools are required to evaluate the cardiac risk of obese patients. However, standard myocardial imaging with SPECT MPI and echocardiography may have technical difficulties in some patients with obesity (27–30). In the present study, ^{82}Rb PET MPI distinguished cardiac event risk in obese patients with known or suspected CAD. The annual hard cardiac event rates were 0% in those with a normal SSS and 6.0% in those with an abnormal SSS, indicating low and high risk, respectively (5,7,51).

The high spatial resolution and attenuation correction of PET help explain the current findings in the obese population (11). The current study supports the clinical utility of ^{82}Rb PET MPI in patients with obesity.

Study limitations. In the present study, the total hard event rate was low, at 4.6% in the overall study population. However, this hard event rate is similar to previous SPECT studies, which range between 2.6% and 5.5% in patients with suspected or known CAD (3,21,45,46,52). Our sample size and number of hard cardiac events were smaller. However, these were sufficient to detect significant differences in hard and total cardiac event rates among ^{82}Rb PET MPI SSS groups. Post-hoc sample size calculations showed a power >80% with the univariable unadjusted survival analysis log-rank test for these comparisons.

The multivariable Cox proportional hazard models are limited by the number of events. Accordingly, to prevent overfitting of the multivariable Cox proportional hazard models, we reduced the number of variables entered into the model as described in the statistical methods section. With the adjusted model for cardiac death and nonfatal MI only containing three variables (SSS, age, and history of MI), the benefits of 10 events per variable are almost achieved. With the adjusted model for total cardiac events containing four variables and more than 10 events per variable, the results are more powerful. Post-hoc sample size calculations for the adjusted models for total events and hard events showed the power to be 83% and 64%, respectively. Statistically significant differences in the event-free survival (for both total events and hard events) were observed in the current study. However, an adjusted model approach for hard events in future studies may require a larger sample size.

In the current study, 8.3% of patients were lost to follow-up. This is somewhat higher than some but is similar

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to other previous reports, with rates ranging from 3.8% to 7.0% (3,21,32,45). This may in part be related to the timing of follow-up, which was longer than in most previous SPECT studies, and to the fact that some of our patients are referred from other centers and regions, which can sometimes make follow-up more difficult. Although it is not possible to determine whether events occurred or not, the similarity with the main population suggests that there was no bias of demographic or SSS among the patients who were lost to follow-up.

Recently, electrocardiogram gated acquisition has been applied to PET MPI; this as well as left ventricular mass and flow measurements may add value to PET imaging data. However, measurement of left ventricular mass, flow quantification, and gated acquisition were not routinely performed when these patients underwent their PET imaging in the year 2000. Thus data on these parameters are not available.

The SPECT subgroup was a selective population; therefore, the data must be interpreted with caution. The sample size was small but still large enough to show a significant difference in total cardiac event rates for normal compared with abnormal ^{82}Rb PET MPI. Post-hoc sample size calculations showed a power >80% with the univariable unadjusted survival analysis log rank test for this comparison. The small number of events in this subgroup limited the ability to perform the multivariable analysis. Events in this subset were predominantly revascularization or hospitalization. Berman et al. (21) reported that increased total cardiac events among patients with equivocal SPECT were also predominantly revascularizations. Further study with a larger sample size is required in this population.

The sample size for the obese subgroup was also small. However, post-hoc sample size calculations also showed a power >80% with the univariable unadjusted survival analysis. Although, the present data show significant differences in hard and total cardiac event rates for normal compared with abnormal ^{82}Rb PET MPI, further studies are required with a larger cohorts to confirm our results.

Conclusions. The ^{82}Rb PET MPI has significant prognostic value for predicting cardiac events. Normal-perfusion PET carries an excellent prognosis. With the adjusted survival model, ^{82}Rb PET SSS was the strongest predictor of total cardiac events and was also a significant predictor of hard cardiac events. The ^{82}Rb PET MPI also seems to have prognostic value in patients whose diagnosis remains uncertain after SPECT MPI and in patients with obesity. The prognostic value of PET MPI may improve the management of cardiac patients.

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